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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,308	10/24/2003	Frank Grosveld	CARP0015-100	1498

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SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/693,308	**Applicant(s)** GROSVELD, FRANK	
	Examiner Anoop Singh	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4,7,8,10,11 and 33-36*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, AU 1632

see attached sheet

Continuation of 3. NOTE: The proposed amendments to claims 2, 4, 7-8, 10, 36 and arguments are not persuasive to overcome outstanding rejections of the record, because the proposed amendments to the claims read on a method of producing of a single heavy chain antibody in a non-human mammal comprising the step of expressing a heterologous VHH heavy chain locus in that mammal specifically in B cells by "using a regulatory sequence"e providing for expression of the VHH heavy chain locus, wherein locus regulatory sequence is a "locus control region". These proposed amendments alters the scope and includes a new limitation which was neither required nor recited in previously rejected claims. This altered scope of producing single heavy chain antibody in a non-human mammal would require new search and additional considerations. In additon, it is noted that proposed amended claim 4 step (a) recite a typographical error "..at least one one D exon", which shlould be changed to recite "at least one D exon".

Continuation of 5. Applicant's reply has overcome the following rejection(s): Claims 1-4, 7-8, 10-11 and 33-36 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 7-8, 10-11 and 33-36 of copending Application No. 10/692,918 is withdrawn in view of terminal disclaimer filed on June 25, 2007.

Continuation of 11: The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
The Examiner maintains the rejection of claims 1-4, 7-8, 10-11 and 33-36 under 35 U.S.C. 112, first paragraph and 35 U.S.C. 112, second paragraph, for the reasons of record. Applicants rebut the rejection of the claims under 35 USC 112, first paragraph, 35 USC 112, second paragraph and 35 USC 102(b) in the reply filed 6/25/2007.
Applicant arguments filed on 06/25/2007 have been fully considered but they are not fully persuasive because the claim amendments have not been entered since proposed claim amendments require new consideration and search.
Claims 1-4, 7-8, 10-11 and 33-36 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record.

Applicant arguments filed on 06/25/2007 have been fully considered but they are not fully persuasive because the claim amendments have not been entered since proposed claim amendments require new consideration and search . To the extent arguments apply to the pending claims, Applicant arguments filed on 06/25/2007 have been fully considered but they are not fully persuasive. Applicants rebut the rejection of the claims under 35 USC 112, in the reply filed 06/25/2007, citing instant claims are fully enabled. It is noted that instant claims are directed to a method for the production of a single heavy chain locus in an mammal specifically in response to antigene challenge leading to formation of a single chain antibody. Applicants cite post-filing art in support of enablement showing Applicants have generated both IgG and IgM heavy chain only antibodies in mice following the disclosure of the specification as filed. Specifically, the cited paper discloses the expression of loci containing IgM and IgG, and IgG only, human constant regions, lacking CH1, with two camelid VHH regions, and human D and J regions in mice. Bac clone 11771 and pFastBac were used successfully and the loci further contained FRT and LoxP sites, and immunoglobulin LCR. The vectors are injected into fertilized mouse eggs of animals that do not produce surface IgM and have a block in B cell development at the pre-B cell stage and in wild type mouse.

In response, it is emphasized that instant claims are not directed to a method of producing transgenic nonhuman mammal comprising any vector rather claims are directed to a method for the production of single heavy chain antibody specifically in B cells in response to an antigen challenge. Upon further review of post filing art, examiner would agree that instant specification discloses necessary elements in the specification, however, fails to support the full breadth of independent claim 1. For instance, applicant's claims post filing art teaches injecting vectors into fertilized mouse eggs of animals that do not produce surface IgM and in wild type mouse. However, Examiner could only find support for B220 CD19-positive BM cells of GΔ line1 transgenic mice in a WT background exhibit that B cells express either mouse IgG or chimeric IgG showing allelic exclusion (Figure 3C). Janssens et al (2006, art of record) describe BM cells express either mouse or chimeric cell surface Ig, wherein few BM cells expressed both on the surface (Fig. 3*F*). This would only indicate that GΔ

transgenic mice in WT background would either express mouse IgG or chimeric IgG. However, it does not support the breadth of instant claims that are directed for the production of a single heavy chain antibody in any nonhuman mammal comprising a heterologous VHH heavy chain locus in response to an antigen. In fact, the post filing art (Janssens et al, 2006, IDS) upon which applicants are relaying for enablement supports a method that use GΔ/ μMT mice for immunization with *Escherichia coli* hsp70, DKTP to generate single heavy chain antibody (see page 15133, col. 2, para. 4 and 5). In view of preceding discussion it is clear that method for the production of single heavy chain antibody in response to an antigen as disclosed in the post filing art do not support enablement for the breadth of pending claims, rather post filing art teaches a method that use transgenic GΔ/ μMT mice for immunization with *Escherichia coli* hsp70 for the production of single chain heavy antibody.

In response to applicants argument that LCR functions across all species, it was indicated by Examiner in final rejection that the method upon which applicant relies uses specific vector, LCR elements that is injected into a fertilized mouse egg of an animal that do not produce surface IgM and have a block in B cell development at the pre-B cell stage which is neither required on recited in the instant claims. It is emphasized that instant claims read on expressing vectors of the present invention into any animal to produce a nonhuman mammal comprising the step of expressing a heterologous VHH heavy chain in response to an antigen. The specification teaches, "animal may be ... mammal, preferably, a non-human mammal such as a rodent and even more preferably a rat or mouse. In this regard, it is also preferred that the recipient animal is incapable of producing antibodies that include light chains or at the very least has a reduced capacity to produce such antibodies" (see para 128 of the published application). The guidance provided by the applicants gives invitation to others to try different existing transgenic knockout nonhuman animals incapable of producing antibodies that include light chains to express VHH heavy chain loci as contemplated in the instant application. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The art teaches variable effects of different promoters depending upon

site of expression. This is supported by numerous studies showing that given construct may react very differently from one species to another. The specification only provides general guidance for using tissue specific promoters (supra). In fact applicants cited post filing art of Janssens et al also describe the difference in results from those obtained by Zou et al with respect to the role of LC rearrangement *(*J Immunol, 2005, 175*:3769–3779)* to level of expression of the locus (and, thus, signaling). Janssens et al attributes this difference in results to use of LCR in the constructs (see page 15134, col.2, para.1). In absence of any specific guidance and given species-specific differences in the expression of various transgenes, an artisan would have to perform undue experimentation and make new inventions in order to practice the method as claimed. In the instant case, the specific elements contemplated by the specification in the construction of vector, promoters, regulatory sequence and background μMTmouse for use in production of a single heavy chain antibody in response to antigen challenge in an animal were not discovered by Applicant, rather they were derived from the prior art based on reports of their function in mice. Absent of evidence to the contrary, it is not clear that these elements would be functional in other nonhuman mammal species in the same manner as they have been demonstrated in the transgenic mouse in a specific background. Given such differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic nonhuman mammal expressing VHH heavy chain locus in B cell in response to antigen challenge leading to formation of single heavy chain antibody, it would have required undue experimentation to establish the levels of the transgene product, the consequences of that product (see Janssens and Zou supra). It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994),* citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).* An artisan would have to perform undue experimentation to determine the appropriate tissue specific promoter or

locus control regions (LCR) that would specifically express VHH heavy chain locus specifically in B cell of any nonhuman mammal.

Claims 1-4, 7-8, 10-11 and 33-36 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps for the reasons of record.

Claims 1-2 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ledbetter et al (WO 99/42077, dated 08/26/1999, IDS) for the reasons of record.

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